REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-22 are pending. The title and abstract are amended to correct informalities, to be more descriptive, and to improve clarity. Similarly, the claims are amended to correct informalities, to improve clarity, and to address the objections on page 3 of the Office Action. Some of the informalities noted by the Examiner were created during the optoelectronic scanning of claims 5 and 15 when they were presented in the Preliminary Amendment. The informalities were not present in the original claims. Claims 5 and 15 are presented here in their correct form. Withdrawal of the objections is requested.

Claims 5, 14 and 16 were rejected under Section 112, second paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse. As noted above, claim 5 was terminated with a period as originally presented. Claim 14 is amended to clarify that the limitation is to local treatment of the GI tract. Claim 16 is amended to recite a positive step of the method of treatment. Applicants request withdrawal of the Section 101 and 112 rejections because the pending claims are clear and definite.

Background of the Invention

A novel drug delivery system involves on a new dosage, new administration routes which would lead to effective therapeutic effects. The medication should be relatively cheap to manufacture, offer convenient form of drug administration, and reduce the possibility of errors in the total dose.

Usually, oral administration of a drug is the least predictable route of administration, yet the most frequently used one. Use of oral controlled release drugs is the most convenient. Controlled drug delivery also usually results in substantially constant blood levels of active ingredients as compared to the fluctuations observed with immediate release dosage forms.

Preparation of novel dosage forms depends on many factors like route of administration, properties of the therapeutic agent to be administered, effective and safe blood levels of the drug, absorption window (absorption site in the gastrointestinal tract), etc.

Drugs meant for oral administration may be formulated as immediate release dosage forms or controlled release dosage forms. Controlled release dosage forms increase the efficiency of treatment and improve patient compliance. Various designs of controlled release dosage forms are reported that differ in their mode of operation.

The novelty and nonobviousness of an invention in this field lies in its mode of operation, design of dosage form, use of a particular class of excipients, use of one or more known excipients in a particular combination, use of novel excipients or a combination of excipients, use of particular modes of addition of excipients or use of different levels of excipients, use of a combination of excipients to prepare one or more layered formulation each having a particular property thereby providing the final formulation with some desired beneficial properties, different method of manufacture of the dosage form, or any suitable combination of the above to achieve advantages over existing delivery systems. All of the above objectives may be achieved by unique combinations of known excipients in a particular way. The mere fact that one or more excipients are common in two different formulations (for example, a controlled release formulation vs. an instant release formulation of the same drug, to take the simplest of examples or the gastro-retentive floating dosage form of the present invention vs. the pulsating dosage form of Bar-Shalom et al.) does not destroy either novelty or the nonobviousness of the claimed invention. One has to consider the two formulations as a whole and judge them on their merits: i.e., what is the formulation attempting to achieve, whether such a result is expected based on the prior art alone or in combination, whether the prior art provides a direction or in any way motivates or suggests a skilled person to unambiguously arrive at the invention in question, whether the present invention overcomes any problem of the prior art, etc. There are numerous inventions in the formulation space that have several excipients in common, but have been considered to be novel and nonobvious based on the merits of the formulation as a whole and not rejected because one or more excipients are known from the prior art. This includes the fact that some of the common excipients may have been used to perform the same function albeit in a new way or as a part of a novel formulation as a whole.

The Examiner will be well aware of these facts and, therefore, Applicants request that he reconsider his rejections based on the above facts and appreciate the novelty and nonobviousness of their claimed invention in its entirety.

Present Invention

The aim of the present invention is to prepare a pharmaceutical gastroretentive delivery system for controlled release of a therapeutically active agent in the stomach or upper part of the gastrointestinal tract in the form of a bilayer dosage form.

The present invention describes a simpler and a more convenient dosage form, preferably in the form of a bilayer capsule, tablet, or caplet: separate layers for "controlled release" and "prolonged retention" in the dosage form.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1-2 and 4-22 were rejected under Section 102(b) as allegedly anticipated by Bar-Shalom et al. (U.S. Patent 5,213,808). Applicants traverse. The cited '808 patent discloses the following:

1. The dosage form is a pulsatile release dosage system. The article in the cited '808 patent enables the release of the drug at a constant level followed by a pulse of the drug at a predetermined time.
2. The active agents are embedded in all of the layers, however, the first layer contains only the active agent.
3. The controlled delivery of the active agent in the second and subsequent layer is achieved by erosion of the second layer in contact with the aqueous phase, and subsequent release of the active agent from the first layer is through a pulsed release.
4. The second layer consists essentially of a crystalline polymer PEG.

5. The geometric form of the formulation in the cited '808 patent is important for obtaining the desired pulsatile release (column 14, lines 42-44).

In comparison to the disclosure of the '808 patent, the present invention requires the following delivery system:

1. The delivery system described here is a gastro-retentive floating dosage system.

2. The invention describes a bilayer dosage form wherein one layer is primarily responsible for the floating of the dosage form and the other layer containing the active ingredient is responsible for the controlled delivery of the drug. Also the novelty of Applicants' invention lies in the fact that our first layer is swelling controlled and hence they have opted for a water insoluble excipient like ethyl cellulose along with hydrogenated oil. This bilayer dosage form maintains its integrity until complete drug release.

3. The mechanism of delivery of the present invention requires a hydrodynamically balanced bilayer dosage form (e.g., tablet, capsule, or caplet form), wherein one layer comprises low bulk density hydrophobic polymers primarily responsible for floating of the dosage form in the gastric contents and aqueous media leading to gastric retention without necessarily undergoing swelling. Upon coming in contact with the gastric fluids, the dosage form floats on the surface only because of the low density polymers present in the first layer.

4. The active ingredient is present only in an inner layer. The dosage form is a bilayer formulation where one of the layers (outer) is for floating and the other one of the layers (inner) has the drug embedded, from where it is released.

5. The present invention primarily describes a floating system where drug release takes place in a narrow therapeutic window: i.e., in the stomach or upper part of the GI tract.

6. The matrix of the drug containing layer is a hydrophilic polymer (e.g., HPMC) from where drug release takes place after swelling, and drug release is prolonged at the particular narrow therapeutic window.

7. The formulation of the present invention is not limited to any particular geometrical form (cf. Figs. 1 to 6 of the '808 patent).

Therefore, it is quite apparent that the two delivery systems are entirely different in terms of composition, methods of delivery, and mechanism for achieving the desired delivery. A mere commonality of one or two excipients cannot be considered to anticipate the present invention since one has to look at the invention in its entirety while considering anticipation as well as obviousness. Novelty of an invention is not destroyed by the mere fact that some of the excipients in the formulation are similar though the entire mechanism and the basic delivery technology of the formulation are different.

Withdrawal of the Section 102 rejection is requested because the cited document fails to disclose all limitations of the claimed invention.

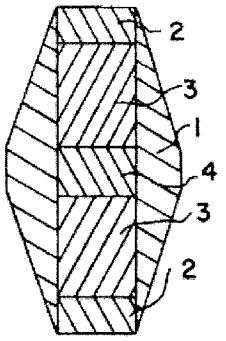
35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing the legal standard provided in *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness under Section 103(a) requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn*, 78 USPQ2d at 1335; see *KSR*, 82 USPQ2d at 1396. A claim which is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. at 1396. Finally, a determination of prima facie obviousness requires a

reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1-15 and 17-22 were rejected under Section 103(a) as allegedly unpatentable over Bar-Shalom et al. (U.S. Patent 5,213,808). Applicants traverse.

The cited '808 patent discloses a pulsatile dosage form which is illustrated as an exemplary embodiment in the following drawing:



The above is a cross sectional view of the formulation (see Figs. 1 to 6 of the '808 patent). It is a multilayered composition where all the layers consist essentially of the same or a different active ingredient. Delivery occurs as follows:

- there is an initial burst release of the drug from layer 2 in large amount,
- then layer 3 is eroded constantly (layer 3 may or may not consist of the same or the different active ingredient), and
- finally the core layer 4 also undergoes a burst release of the drug embedded in that particular layer thereby releasing the (same or different) drug in large amount.

Layer 1 is an enteric coated polymer which helps in the release of the drug at a predetermined time. Hence, the cited '808 patent discusses the pulsed release of one or more different active substances at different time intervals.

Whereas, in the present invention, the mechanism is entirely different. Applicants teach a floating system where there is a sustained and prolonged release of one particular drug in a specific therapeutic window through a hydrodynamically balanced mechanism. The pulsatile dosage form of the '808 patent does not have (1) a first layer responsible for retaining the dosage form in the stomach or upper part of the gastrointestinal tract (spatial control) for a prolonged period and (2) a second layer which is

responsible for prolonged or controlled drug delivery (temporal control) of the therapeutically active agent. There is no such "first layer" taught or suggested in the '808 patent (cf. claim 1 of the present application) nor does the dosage form float on the surface of the gastric fluid for a period from 0.5 to 10 hours (cf. claim 19 of the present application). Moreover, the specific ratio of ethylcellulose and hydrogenated oils recited in claim 3 of the present application is neither taught nor suggested in the '808 patent.

To constitute anticipation, all the claimed elements must be found in exactly the same situation and united in the same way to perform the identical function in a single unit of the prior art. It has been said that, "No doctrine of the patent law is better established than that a prior patent or other publication to be an anticipation must bear within its four corners adequate directions for the practice of the patent invalidated." Anticipation can only be established by a single prior art reference which discloses each and every clement of the claimed invention. In the present case, however, the cited '808 patent does not teach most of the components of the present invention (except for the commonality of one or two excipients, which the prior art discloses as optional ingredients). As will be further discussed below, the failure of the '808 patent to teach the claimed invention is not addressed by any articulated reason in the Office Action for modifying the prior art disclosure to result in the claimed invention with any reasonable expectation of success.

It is clear that Applicants' claimed invention and the disclosure of the cited '808 patent are entirely different. The mere similarity and disclosure of one or two excipients does not render obvious the invention. What actually matters is whether the use of the particular component/excipient is for same or other purpose, what role the excipient has in the overall delivery system, and whether the role of the excipient is critical as to make it the basis for determining the nonobviousness of the formulation.

The cited '808 patent discloses a pulsatile delivery dosage form where the same or different drug(s) are delivered in pulses at specific time periods. This is accomplished by a multilayer composition in which all the layers have the active substance. There is a constant release of the drug followed by a pulse of drug after a predetermined time. The

dosage form is particularly useful for treatment of diseases like rheumatoid arthritis or related disorders with non steroidal anti- inflammatory agents.

In contrast to the above, Applicants' claimed invention relates to a bilayer dosage form exerting its therapeutic effect at the upper part of the GI tract, which "floats" as discussed above. Here, there is no pulsatile release of drug; in fact, the drug is released in a controlled and sustained manner for a prolonged period of time at a constant level. Hence, when the basic fundamental delivery system of the invention is different from the cited prior art, then there cannot be any issue of obviousness because there would be no reason to make modifications resulting in the claimed invention, just for the mere fact of similarity of one or two excipients.

In the cited '808 patent disclosing the pulsatile dosage form, ethyl cellulose and oils are used as fillers. But the purpose for using these excipients is different from that of the present invention. In the cited '808 patent, they may be used along with the matrix as fillers for controlled erosion and the better stability of the formulation. In Applicants' claimed invention, however, the same excipient is used for a different mechanism. It is used as a low density polymer for the floating of the dosage form. This particular excipient is used to obtain a hydrodynamic balanced system having an entirely different mechanism of delivery than that disclosed in the cited '808 patent which is a pulsed delivery. This difference is an essential component of Applicants' invention.

Applicants submit that there are many instances where the same ethyl cellulose is used in combination with hydrogenated oil in a patented composition, but for different purposes, different mechanisms of delivery, and different dosage forms.

US RE39,043 describes a collagen producing promoter composition where, in a particular formulation, ethyl cellulose and hydrogenated oil are used as thickeners.

US 7,141,249 describes a rapidly soluble drug composition, where the same excipients are used but ethyl cellulose is a binder and the hydrogenated oil is a lubricant. Hence, in this formulation, the same excipients are also used. But they are used for a different purpose and a different formulated product is formed.

US 7,214,387 describes a sustained release composition of metformin. Here, the coating consists of a combination of the same excipients, but they serve the different purposes of contributing hydrophobicity and retarding the rate of release.

There are numerous other examples where formulations using similar excipients have been granted patents where the same or similar excipients have been used for a different purpose in obtaining different delivery systems having different mechanisms of action. Applicants emphasize that their claimed formulation has to be looked at in its entirety to determine novelty and nonobviousness, and not on the basis of similarity of one or more components in the formulation.

Withdrawal of the Section 103 rejection is requested because the claimed invention would not have been obvious to the ordinarily skilled artisan at the time Applicants made their invention.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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